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DOI:

[10.1016/j.ejso.2018.08.026](https://doi.org/10.1016/j.ejso.2018.08.026)

Document Version

Peer reviewed version

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Citation for published version (APA):

Schilling C, C., Gnansegaran, G., Thavaraj, S., & Mark McGurk, G. (2018). Intraoperative sentinel node imaging versus SPECT/CT in oral cancer – a blinded comparison. *European Journal of Surgical Oncology*.
<https://doi.org/10.1016/j.ejso.2018.08.026>

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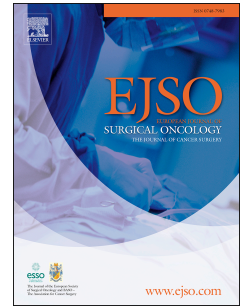
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Accepted Manuscript

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PII: S0748-7983(18)31302-7

DOI: [10.1016/j.ejso.2018.08.026](https://doi.org/10.1016/j.ejso.2018.08.026)

Reference: YEJSO 5080

To appear in: *European Journal of Surgical Oncology*

Received Date: 4 March 2018

Revised Date: 16 June 2018

Accepted Date: 7 August 2018

Please cite this article as: Schilling C C, Gnansegaran G, Thavaraj S, Mark McGurk G, Intraoperative sentinel node imaging versus SPECT/CT in oral cancer – a blinded comparison, *European Journal of Surgical Oncology* (2018), doi: 10.1016/j.ejso.2018.08.026.

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Intraoperative sentinel node imaging versus SPECT/CT in oral cancer – a blinded comparison.

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Keywords

Oral cancer

Sentinel node biopsy

Cervical metastasis

Lymphoscintigraphy

SPECT/CT

Freehand SPECT

Abstract

Introduction

Sentinel node biopsy (SNB) is gaining popularity as a staging tool in oral cancer. Protocol mandates radiotracer injection and pre-operative imaging (LSG +/- SPECT/CT) in the nuclear medicine department. This approach limits application to accessible tumours and to centres with nuclear medicine. New technology, freehand single photon emission computed tomography (fhSPECT), has proved a useful adjunct in intraoperative imaging and localisation of sentinel nodes. This study investigates fhSPECT as an alternative to traditional imaging, an approach that would widen the remit of SNB.

Methods

Fifty consecutive cT1-T2 N0 oral cancer patients received radiotracer followed by lymphoscintigraphy and SPECT/CT. Surgery was undertaken using fhSPECT by a surgeon blinded to pre-operative imaging. Prior to biopsy completion, results of pre-operative imaging were reviewed and any additional nodes removed. The accuracy of LSG, SPECT/CT and fhSPECT were compared.

Results

Nineteen patients had positive sentinel nodes. Disease free survival for sentinel node positive versus negative was significant ($p < 0.005$)

All modalities missed positive nodes in at least one patient. The false negative rate for lymphoscintigraphy, SPECT/CT and fhSPECT was 26.3%, 15.8% and 5.3% respectively.

Discussion

These data show a surgeon naïve to the results of traditional pre-operative sentinel node imaging can use fhSPECT in the operating theatre to accurately locate sentinel nodes in oral cancer. Freehand SPECT showed excellent sensitivity and a low false negative rate offering the possibility of a streamlined intraoperative sentinel node protocol.

1 Introduction

The complex nature of lymphatic drainage within the head and neck means that intraoperative identification of sentinel nodes (SNs) is always informed by pre-operative imaging, traditionally lymphoscintigraphy (LSG) and/or Single Photon Emission Computed Tomography (SPECT)/CT[1-4]. These imaging modalities are outpatient based, with radiotracer injection up 24 hours prior to surgery[1, 5]. Results of multiple sentinel node biopsy (SNB) studies have shown promising results in early oral cancer with large studies reporting overall sensitivity 88-97% in detection of occult neck metastasis[2, 3, 6, 7]. Detection rates vary depending upon the imaging modality used, with the sensitivity of LSG ranging between 81-93%, and SPECT/CT 93-100%[8-11]. These imaging modalities have proven utility but disadvantages include requirement for expensive gantry based equipment, long imaging times (up to 90 minutes), multiple staff members involved, and the tumour must be readily accessible to inject[12]. New more flexible technology (e.g. freehand SPECT, hand-held gamma cameras) may be used to allow intraoperative SN imaging thus reducing the cost of the pathway as well as opening the technique to deeper tumours that are only accessible with the patient under general anaesthetic[13-15].

A recently described method of imaging by freehand SPECT (fhSPECT) allows real-time intraoperative lymphoscintigraphic mapping for SNB combining a hand-held detector (traditional gamma probe) with a patient-tracking device[16-18]. Gamma counts recorded by hand-held probe 'scanning' the patient from different angles are processed by iterative algorithms to produce a three-dimensional (3-D) map of radiation hot spots. These data are combined with contemporaneous video recording, producing an augmented reality (AR)

composite image of the patient and superimposed radiation signal. The user can switch between AR and 3-D navigation mode to localise sentinel nodes during surgery. The advantage of fhSPECT is the ability to build up a dynamic mapping within the region of interest, not limited to a specific field of view, that can move with changes in the patient's position during surgery. It also allows for re-scanning during the procedure to reflect changes in anatomy.

Review of the literature reveal a small number of case reports and pilot studies using fhSPECT for SNB detection in breast cancer[16, 18-21], melanoma[22, 23] prostate cancer[24, 25] oropharyngeal tumours [26] and oral cancer[27, 28].

Two publications present case series in oral cancer. Bluemel et al.[29]published a series of twenty-three oral cancer patients in whom pre-operative scanning by fhSPECT had a 98% detection rate (out performing lymphoscintigraphy but not SPECT/CT) however, the investigators were not blinded to the results of the conventional nuclear medicine imaging prior to scanning with fhSPECT [30].

Additionally all patients had concurrent neck dissection, potentially masking any failings in the technique. Heuvleing et al.[31] published a case series of 66 patients with cT1-T2 N0 oral cancer who underwent SNB using fhSPECT. In this study fhSPECT identified 94% of the sentinel nodes that had been identified pre-operatively, however it should be noted that the position of the nodes had been marked on the neck by the nuclear medicine team prior to the surgeon scanning with the fhSPECT system. Investigators asked the surgeons to rate on a three-point scale the usefulness of the system in identifying and retrieving the nodes during surgery, and found that it provided additional useful information in 24% of cases

To date fhSPECT has only been investigated as an adjunct to traditional sentinel node imaging rather than an independent localisation modality for SNB. However, if fhSPECT proves accurate enough to localise sentinel nodes without the need for gantry-based outpatient imaging, the whole procedure could be undertaken in the operating theatre thus reducing the time and cost incurred. If successful, this would open the application of SNB to tumours that are only accessible for injection with radiotracer once the patient is under general anaesthetic.

This study aims to assess whether fhSPECT guided sentinel node biopsy can be accurately undertaken in patients with oral cancer by a surgeon who has been blinded to the results of pre-operative LSG and SPECT/CT. The accuracy of three imaging modalities (fhSPECT, lymphoscintigraphy (LSG) and SPECT/CT) are measured by sentinel node identification rate, identification of positive sentinel nodes, and false negative rate. A secondary aim is to understand the optimum post injection window for identification of lymphatic drainage by fhSPECT, thus informing any future protocol that may rely on the intraoperative delivery of radiotracers.

2. Materials and methods

Ethical permission was granted to recruit patients with cT1-T2 N0 oral squamous cell carcinoma (SCC) who were suitable for sentinel node biopsy. Patients have given general consent for images to be used in teaching including publications.

2.1 Outpatient nuclear medicine imaging

Patients underwent peritumoural injection of radiotracer (^{99m}Tc -Nanocoll) up to 24 hours prior to surgery. The total effective dose was 40-80MBq for a two day and 10-20 MBq for a one-day protocol.

Immediate planar imaging was performed using a dual head gamma camera (e.cam, Siemens Healthcare, Munich Germany) using a low energy high-resolution collimator with 9.1mm resolution[32]. Dynamic images were taken in the anterior or oblique view (20 x 60s, 128 x128 matrix). Directly after dynamic imaging static images (120s or 300s, 256 x 256 matrix) were acquired. Patients then underwent SPECT/CT imaging using a dual-detector gamma camera with a mounted 2-row multidetector CT scanner with intrinsic resolution of 3.8mm[33] (Symbia T, Siemens Healthcare). SPECT protocol used 128×128 matrix by 180° in the anterior L-mode rotation with 3° angle step and 20–25 seconds per projection, in 8 iterations, using correction for attenuation and scatter. CT images were obtained by 130kV 17mAs 4.42-5mm slices and reconstructed to sagittal, axial, and coronal views. LSG and SPECT/CT images were analysed by a nuclear medicine physician (GG) and sentinel nodes were identified according to the definition: hotspots that appeared first, were on a direct drainage pathway from the tumour, or contained more than 10% of the activity of the hottest node in the basin[34]. The position of the sentinel nodes were localised on the skin of the neck using a ^{57}Co point-source marker and were marked on the skin. Prior to surgery, imaging was reviewed jointly by GG and one of two surgeons (CS or MM) and the agreed location of sentinel nodes was recorded in a study proforma. The remaining surgeon was kept blinded to the results and took the lead role during the operation. The skin markings were photographed and

removed before the patient was taken to theatre. The surgical approach was entirely based upon intraoperative fhSPECT imaging.

2.2 Sentinel node imaging by fhSPECT

Freehand SPECT imaging was undertaken using Declipse®SPECT SurgicEye (GmbH, Germany). Both sides of the neck were scanned until clear images of radiation hotspots were seen or at least 2000 counts were obtained. Sentinel nodes were identified by intensity of signal more than ten times the background radiation (signal to background ratio), automatically calculated by fhSPECT to show a hotspot on the augmented reality and 3-D images. Typical scanning time was 2-3 minutes. Acquired data (scans) were then used to navigate to the sentinel nodes.

The protocol was designed for fhSPECT scans to be taken at two time points “Immediate fhSPECT” – Declipse®SPECT was transported to the nuclear medicine department and scans taken straight after radiotracer injection.

“Intraoperative fhSPECT” - Declipse®SPECT was used in the operating room. Scans were taken immediately before the procedure and subsequently the system was used to navigate to the identified sentinel nodes during surgery.

2.2.1 Immediate fhSPECT

One-third of patients underwent immediate post injection fhSPECT scan performed prior to LSG and SPECT/CT. Freehand SPECT scan commenced five minutes after radiotracer injection. The fhSPECT scan was completed within five minutes but if unsuccessful, no further delay was permitted and the patient

proceeded with standard LSG and SPECT/CT protocol described above, to minimize disruption to the standard care pathway.

2.2.2 Intraoperative fhSPECT

In the operating theatre the lead (blinded) surgeon undertook fhSPECT scan and the position of the identified sentinel nodes were marked on the neck. Intraoperative fhSPECT acquisition took no longer than 5 minutes in each case. Following the image acquisition, the surgeon used both augmented reality and 3-D mode on the device to locate and excise the sentinel nodes. Results of LSG and SPECT/CT were withheld until the sentinel node procedure was completed to the satisfaction of the lead surgeon. The only planned exception to this was in the case of no nodes being found by fhSPECT in which case the pre-operative imaging results were revealed at the beginning of the invasive procedure.

2.3 Surgery

Standard SNB retrieval was undertaken[2] based on fhSPECT results. All retrieved nodes were labelled according to neck level and gamma count.

Once this process was completed and before the neck incisions were closed, the results of the lymphoscintigraphy and SPECT/CT were revealed by the non-blinded surgeon. If there was discrepancy between the pre-operative imaging and the fhSPECT result (nodes not detected by fhSPECT) then the images were reviewed in full by both surgeons on a screen in theatre and a joint decision was made if further nodes required retrieval. All excised nodes were checked ex-vivo

to ensure the gamma count (averaged over 10 seconds) was more than three times the background radiation and more than 10% of the hottest node count. If these criteria were not met the node was considered a non-sentinel node.

Sentinel nodes were processed by serial step sectioning according to published guidelines[1]. In brief, nodes were sectioned at 150 μ m intervals with sections cut at each level. Sections were primarily stained by H&E, if no metastasis were detected immunohistochemical staining with AE1/3 pan-cytokeratin was performed. Metastasis were classified according to size (isolated tumour cells (<0.2mm), micrometastasis (0.2-2mm) and metastasis (>2mm))[35].

Patients were reviewed in clinic one week after surgery. If the biopsy proved positive for metastasis, a completion neck dissection was undertaken.

3. Analysis

Descriptive statistics were used with paired investigations used as the control. Primary outcome, SN detection by each technique (fhSPECT, SPECT/CT and LSG) was compared using one-way repeated measures analysis of variance (ANOVA) analysis.

The second outcome was the detection of positive sentinel nodes. To consider fhSPECT a safe option it should detect all the positive nodes (SN+) that had been found by other methods i.e. 100% concordance between LSG or SPECT/CT and fhSPECT for all SN+ cases.

Univariate survival analysis models were built using Kaplan-Meier product-limit estimator for disease free survival (DFS). Table analysis on outcomes was performed using either chi-square or Fisher's exact to test significance, depending upon the distribution of the variable in question.

4. Results

Between November 2012 and November 2015 fifty patients were recruited to the study. Three patients undergoing SNB declined to enter the study and did not undergo navigation guided SNB by fhSPECT (Figure 1).

Figure 1. Patient recruitment and outcomes.

A total of 144 sentinel nodes were retrieved, an average of 2.88(\pm 2.05) nodes per patient (range 1-8). The sentinel node biopsy was positive for metastasis in 19 patients (38%), in three cases two positive sentinel nodes were identified therefore 22 positive nodes were excised.

Patient and tumour characteristics are shown in table 1.

Table.1 Characteristics of patient and tumour.

	All patients (n=50)	Positive Sentinel node biopsy (n=19)	Effect of variable on sentinel node status
Male	(28/50) 56%	(10/28) 36%	p=0.7
Female	(22/50) 44%	(9/22) 41%	
Age (years median, standard deviation)	61.5 ± 12.08 (range 24- 87)		p=0.61
Positive SNB	(19/50) 38%		
Negative SNB	(31/50) 62%		
Tumour location			
Tongue	(33/50) 66%	(15/33) 45%	p=0.3
Floor of mouth	(8/50) 16%	(2/8) 25%	
Lower alveolus	(3/50) 6%	(0/3) 0%	
Lower lip	(2/50) 4%	(1/2) 50%	
Retro-molar	(1/50) 2%	(1/1) 100%	
Buccal	(2/50) 4%	(0/2) 0%	
T stage (AJCC 7 th Edition, 2010)			
T1	40 (80%)	12/40 (30%)	p=0.02
T2	10 (20%)	7/10 (70%)	
T stage (AJCC 8 th Edition, 2016)			
T1	38 (76%)	9/38 (24%)	p=0.001
T2	9 (18%)	7/9 (78%)	
T3	3(6%)	3/3 (100%)	
N (sn) stage			

N1	(16/19) 84%	
N2b	(3/19) 16%	
Extracapsular spread/ Extranodal Extension		
Yes	(3/19) 16%	
No	(16/19) 84%	

4.1 Immediate fhSPECT scan

Fifteen patients underwent fhSPECT scan. In three cases there was no clear drainage to the neck. In a further two cases there was drainage seen to the neck but the signal could not be isolated to a discrete area. The remaining ten cases had hot nodal areas detected that could be grouped into three patterns:

- i) No discernable drainage on immediate fhSPECT scan with clear drainage shown on subsequent scans (Fig 2A).
- ii) Clear drainage seen on immediate fhSPECT scan, but further drainage found on subsequent scans (Fig 2B).
- iii) Clear drainage seen on immediate scan with no additional hotspots found on subsequent scan (Fig 2C).

Nine of the fifteen patients proved to have positive sentinel nodes by histopathological analysis (60%). The positive sentinel node was located by immediate fhSPECT in only three of these cases, thus the sensitivity for detection of positive sentinel nodes was 33% and the false negative rate 40% (Table 2).

Table 2: Cases that underwent immediate freehandSPECT (fhSPECT) scan following injection of radiotracer. FOM= Floor of mouth. * denotes sentinel node that was found to contain metastasis.

Case	Side of body	Tumour location	Dose of Nanocolloid (MBq)	One or two day protocol	Immediate fhSPECT result	SNB Result
1	Left	Tongue	20	One	Indeterminate drainage left neck	Positive
2	Left	FOM	20	One	Left and right submental and right IIa	Negative
3	Right	Tongue	20	One	Right level IIa	Negative
4	Right	Tongue	85	Two	Right level IIa and Right level III	Negative

5	Right	Tongue	20	One	Right level IIa	Positive
6	Left	Lower lip	20	One	Right and left Ib and left facial	Negative
7	Left	Tongue	33	One	Left level IIa *	Positive
8	Right	Tongue	19	One	Right level II/III*	Positive
9	Left	Tongue	17	One	No nodes found	Positive
10	Left	Tongue	20	One	Left Ib* Left IIa Right IIa	Positive
11	Left	FOM	20	One	No nodes found	Negative
12	Right	Lower lip	20	One	Left and right facial, Left IIa	Positive
13	Midline	FOM	54	Two	R submental, right facial, Right III	Negative
14	Midline	FOM	53	Two	Indeterminate drainage right and left neck	Positive
15	Left	Tongue	69	Two	No nodes found	Positive

Examples of cases are shown below (Figure 2) these demonstrate characteristic high signal and scatter which is found at the tumour site immediately post injection.

Figure 2. Patterns of drainage found on immediate post injection fhSPECT scan compared to pre-operative fhSPECT (2-24 hours post injection)

4.2 Blinded fhSPECT compared to lymphoscintigraphy and SPECT/CT

Of the 144 sentinel nodes excised 95 were identified by lymphoscintigraphy, 122 by SPECT/CT and 125 by fhSPECT. A sample case is shown in figure 3

Figure 3. Sentinel node identification by SPECT/CT and lymphoscintigraphy versus fhSPECT. All modalities found three sentinel nodes. Neck markings by nuclear medicine (left) and surgeon (right) can be compared

A one-way repeated measured analysis of variance (ANOVA) was conducted to evaluate the null hypothesis that there is no difference in the number of sentinel nodes localised by each modality. The results of the ANOVA indicate a significant effect, Wilks' Lambda $p < 0.001$. Follow up comparisons indicated that pair-wise

difference between lymphoscintigraphy and both SPECT/CT and fhSPECT were significant ($p=0.002$) but comparison between SPECT/CT and fhSPECT were not ($p=1.000$).

Lymphoscintigraphy failed to show any drainage in four patients. SPECT/CT showed no drainage in one patient and fhSPECT showed drainage in all patients. In two cases the surgical plan was changed after revealing the results of the SPECT/CT. In both cases further nodes were localised and excised. These nodes were negative for metastasis.

There were no false negative results (neck recurrence after negative SNB) at minimum 24 months follow up. However, all modalities missed positive nodes in at least one patient (Table 3). The false negative rate (FNR) was estimated for each imaging modality calculated as: $\text{true positive} / (\text{true positive} + \text{false negative})$. In this study a true positive result was encountered when an imaging modality identified sentinel nodes subsequently found to contain metastasis. A false negative result was recorded when an imaging modality failed to detect a sentinel node subsequently found to contain metastasis. The FNR was calculated on a per case rather than per node basis as the neck status correct biopsy result, neck status, only requires one positive node (i.e. a patient with one positive or more than one positive sentinel node will be treated the same, by completion neck dissection). The FNR for lymphoscintigraphy, SPECT/CT and fhSPECT was 26.3%, 15.8% and 5.3% respectively. If we consider the hypothetical situation that all the positive nodes missed were left until clinically apparent the overall neck control rate (NCR) for each modality in this cohort (fifty patients, three

regional recurrences) would be 84%, 88% and 92% for LSG, SPECT/CT and fhSPECT

Table 3. Number of positive nodes found by each modality

	Missed positive cases (n=19)	False negative rate	Neck control rate
LSG	5	26.3%	84%
SPECT/CT	3	15.8%	88%
fhSPECT	1	5.3%	92%
Total cohort (all modalities)	0	0%	94%

Freehand SPECT failed in to identify a positive node in one patient with a tongue tumour. The pre-operative fhSPECT scan identified a facial node and a level IIb node. Both pre-operative SPECT/CT and LSG found two hot areas in the left neck - level IIa and level III - of which the level IIa node was positive for metastasis.

4.3 Survival

Median follow up was 65 months (range 21-119 months). Five patients died from disease recurrence (three in the neck, two with distant metastasis), all were in the sentinel node positive group. Disease free survival for sentinel node positive versus sentinel node negative was significant ($p<0.005$)

5. Discussion

Immediate fhSPECT was performed in 30% of the study group and provided new information in this field of investigation. The reason that not all patients could be

scanned immediately post-injection was due to clashing scheduling of both surgery and injection. Often, more than one SNB cases would be scheduled per day therefore the equipment was in use in theatre at the time that the second patient was undergoing injection.

Nevertheless the experiences gained showed that immediate fhSPECT (< 10min post injection) is not reliable, with a false negative rate of 40%. This can be explained by the high level of signal at the injection site immediately after injection resulting in signal scatter and shine through effect masking signal tracking to the sentinel nodes.

This study protocol did not allow delay of more than ten minutes between injection of the tracer and commencement of lymphoscintigraphy. This is due to historical concern about the risk of missing in-transit sentinel nodes. These are defined as nodes which the tracer completely passes through en-route to second echelon nodes, and can escape detection if only late images are taken. In-transit nodes are recognised as rare occurrences and have been reported in melanoma but there are no reports of this situation occurring in oral cancer[1, 36, 37].

In this study the performance of fhSPECT, particularly in the immediate post injection period was unknown and so the study was designed to alter the standard imaging pathway as little as possible.

What has been shown clearly by these results is that lymphoscintigraphy performed poorly compared to both SPECT/CT and fhSPECT in the detection of SNs ($p<0.005$). There was no additional benefit to performing LSG (i.e. it did not identify nodes missed by other modalities) thus opening up the possibility that LSG could be omitted allowing serial fhSPECT scans to be taken in the immediate period following injection. SPECT/CT is normally performed after the LSG

protocol is finished, usually 90 minutes following injection. A future protocol for consideration is fhSPECT scan at ten-minute intervals post injection followed by SPECT/CT at 90 minutes. This would assess the real-time tracking capabilities of fhSPECT. The results of such an investigation would inform how applicable fhSPECT is to a purely intraoperative technique where it is imperative that the surgical flow is not interrupted for prolonged periods to allow drainage

FreehandSPECT showed excellent sentinel node identification when used as an intraoperative tool, however it did miss a positive sentinel node in one case. In this patient two hotspots had been identified in the left neck by all three modalities, LSG and SPECT/CT localised to level IIa and III whereas fhSPECT showed a facial node and a level IIB node. When the gamma probe was used independently of the navigation mode during the procedure, sentinel nodes were retrieved from level IIb and III. This suggests that there was a co-registration problem between the gamma probe and patient tracking device, leading to incorrect reconstruction of the gamma signal in three-dimensions.

In this case a potential explanation is that the head position (and thus the patient tracking device) was moved during the data collection. The tracking device is attached to the forehead and will map accurately when the head is rotated in a neutral position however if any lateral flexion of the neck is introduced the relationship between the nodal hotspots and patient tracking device is changed and could explain why the nodes appeared to have been shifted superiorly in relation to the actual position.

6. Conclusion

These data show that a surgeon who is naïve to the results of pre-operative sentinel node imaging can use freehand SPECT in the operating theatre to accurately locate sentinel lymph nodes. Freehand SPECT showed excellent sensitivity and a low false negative rate, but a higher detection of negative (possibly non-sentinel nodes). Data collected from immediate post injection fhSPECT is unreliable for SN node detection, suggesting that there is an as yet undefined optimum imaging window for this modality. It remains to be established if this imaging window coincides with a time frame that is compatible with intraoperative injection and sentinel node retrieval.

Declaration of interest: none

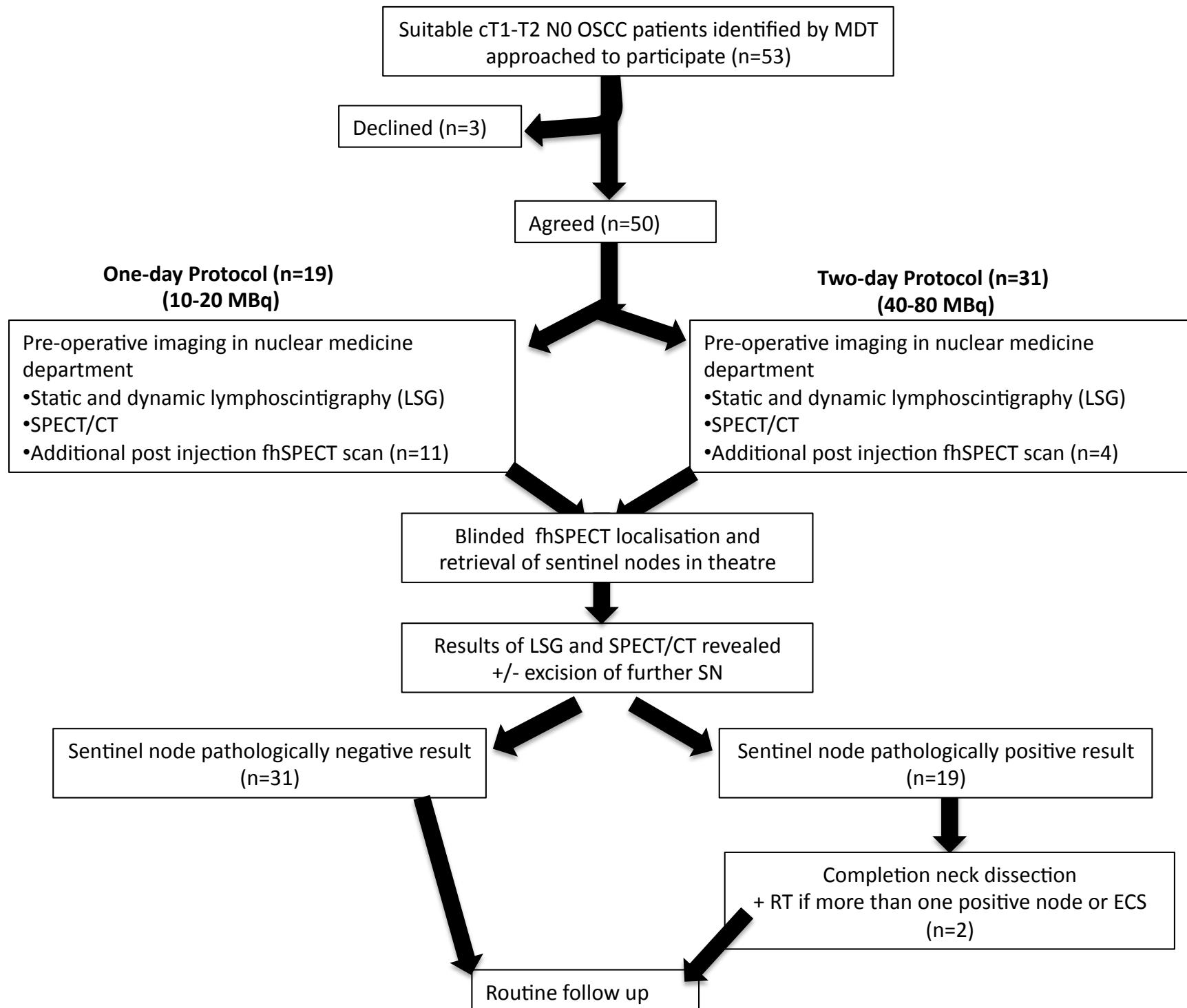
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SPECT/CT

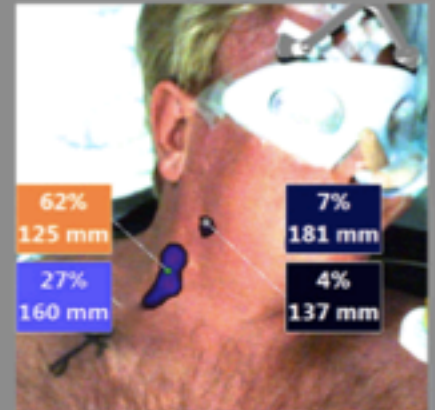


Lymphoscintigraphy



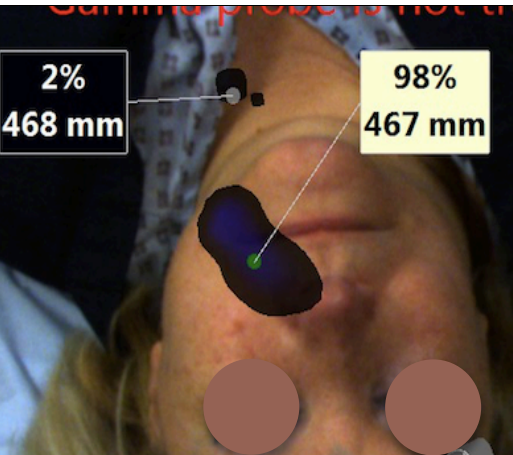



Pre-operative marking using ^{57}Co point-source marker by nuclear medicine physician

Pre-operative fhSPECT



Pre-operative marking by blinded surgeon based on fhSPECT scan

Immediate freehandSPECT scan	Pre-operative freehandSPECT scan (2-24 hours post injection)
A 	
B  <p>2% 468 mm</p> <p>98% 467 mm</p>	
C 